

A Prospective Investigation of Height and Prostate Cancer Risk

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Abstract

Greater adult height, which reflects a combination of early nutrition, exposure to androgens, growth hormones, and other factors during growth and development, as well as heredity, has been associated with increased prostate cancer risk in several observational studies, but findings have been inconsistent. We examined this relationship in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort. At baseline, 29,119 Finnish male smokers 50 to 69 years old had height and weight measured by trained personnel, provided information on demographic, smoking, medical, and other characteristics, and completed an extensive diet history questionnaire. A total of 1,346 incident prostate cancer cases were identified during a follow-up period of up to 17.4 years (median, 14.1 years). In age-adjusted Cox proportional hazards models, the hazard ratios and 95%

confidence intervals for prostate cancer according to increasing quintiles of height [≤ 168 , 169-171, 172-175, 176-178, and >178 cm] were 1.00 (reference), 1.11 (0.93-1.32), 1.11 (0.95-1.31), 1.30 (1.01-1.55), and 1.14 (0.96-1.35); $P_{\text{trend}} = 0.04$. In analyses stratified by disease stage (available for 916 cases), a strong dose-response relationship was observed between greater height and advanced, but not earlier-stage, disease [tumor-node-metastasis stage III-IV, hazard ratio and 95% confidence interval for increasing quintiles of height: 1.77 (1.18-2.65), 1.82 (1.25-2.65), 1.93 (1.29-2.90), and 2.02 (1.37-2.97); $P_{\text{trend}} = 0.0008$, $P_{\text{interaction}} = 0.002$]. Our study provides additional evidence that increased height is a risk factor for prostate cancer and suggests that taller men are particularly susceptible to advanced disease. (Cancer Epidemiol Biomarkers Prev 2006;15(11):2174-8)

Introduction

Although prostate cancer is the most common cancer and the third leading cause of cancer-related deaths in U.S. males, few well-established risk factors have been identified (1, 2). Incidence increases substantially with age, with $>70\%$ of new cases occurring in men >65 years of age (1). Men from certain racial/ethnic backgrounds (particularly African Americans and Jamaicans) and those with a family history of prostate cancer also have an increased risk of developing the disease (1, 3-5). Prostate cancer seems to have a strong environmental component because migrants from low-risk countries acquire incidence rates that approximate those of men in the host population and because incidence varies >30 -fold between countries (6). Factors under active investigation include diet, physical activity, anthropometric measures [i.e., height, weight, and body mass index (BMI)], growth factors, endogenous hormones, and infectious agents.

Adult height is a highly complex trait that reflects prenatal and early life nutrition and infection, exposure to sex steroids, growth hormones, and other factors during adolescent growth and development, and hereditary predisposition (7). Rapid increases in height during puberty coincide with increases in circulating steroid hormones, insulin-like growth factor-I (IGF-I), and growth hormones, and with prostate gland development (8). Accelerated growth is strongly correlated with greater maximum height (9), and attainment of adult height at an early age has been associated with an elevated risk of prostate cancer in two separate studies (10, 11). Evidence

that puberty may be a critical window for prostate cancer initiation includes the observation of microscopic tumors in 30-year-old men (12, 13).

Height has received attention as a risk factor for prostate cancer over the past two decades, yet the body of epidemiologic evidence about the association remains inconclusive. Case-control studies have reported predominantly weak or no associations (4, 10, 14-26), whereas several cohort studies found statistically significant elevations in risk (27-33). Eight studies have specifically evaluated height as a risk factor for clinically advanced cancer (16, 21, 24, 29-31, 33-35), with three reporting $>50\%$ increases in risk of advanced disease for men taller than 173 cm (24, 29, 30). Because the associations between height and prostate cancer seemed to be relatively modest in the aforementioned studies, large numbers of cases are required to detect small yet meaningful associations.

We investigated the relationship between adult height and subsequent risk of prostate cancer (including advanced disease) in a large, prospective cohort study of male smokers. With $>1,300$ incident prostate cancer cases available for analysis, our study is one of the largest to date examining this association.

Materials and Methods

Study Population. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study was a randomized, double-blinded, placebo-controlled primary prevention trial that tested whether daily supplementation with β -carotene (20 mg) and/or vitamin E (50 mg DL- α -tocopheryl acetate) reduced the incidence of lung and other cancers. A full report of study design, methods, participant characteristics, and adherence has been published (36). The study population consisted of 29,133 male residents of southwestern Finland, ages 50 to 69 years, who smoked five or more cigarettes per day and provided written informed consent before randomization. Subjects with a history of cancer (other than nonmelanoma

Received 6/6/06; revised 8/11/06; accepted 8/21/06.

Grant support: USPHS contracts N01-CN-45165, N01-RC-45035, and N01-RC-37004 from the Intramural Research Program of the NIH and the National Cancer Institute.

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doi:10.1158/1055-9965.EPI-06-0467

skin cancer or carcinoma *in situ*) or other diseases/conditions that might limit full participation in the intervention were excluded. Additional grounds for exclusion were use of vitamin E, vitamin A, or β -carotene supplements in excess of predefined amounts, or receipt of anticoagulant therapy. All subjects were enrolled between 1985 and 1988 and were actively followed until trial closure on April 30, 1993.

The present analysis is based on the 29,119 participants whose height was measured at baseline (99.9% of cohort). Person-years of observation were calculated from the date of randomization to the date of prostate cancer diagnosis, death, or April 30, 2002. The institutional review boards of both the National Public Health Institute of Finland and the U.S. National Cancer Institute approved the study.

Data Collection. Before randomization, participants had their height and weight measured, as well as fasting serum samples collected, by a registered nurse specifically trained for the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Height was measured to the nearest centimeter using a standard medical stadiometer and weight was measured on an electronic floor balance to the nearest 100 g. Detailed information on demographic, medical, smoking, and occupational factors, as well as usual physical activity, was ascertained via self-report, and a validated 276-item dietary questionnaire was completed at baseline. The dietary questionnaire inquired about portion sizes and frequency of consumption of each food item during the past year. A color picture booklet was provided to each participant to assist with portion size estimation.

Case Ascertainment. A total of 1,346 incident prostate cancer cases (ICD-9 code 185) were identified through April 2002. These cancers were identified through the Finnish Cancer Registry and the Register of Causes of Death. For cases diagnosed through April 1999, the medical records were reviewed centrally by two independent clinical oncologists for diagnostic confirmation and staging, and cases with histology or cytology available were also reviewed and confirmed by one or two study pathologists. Information on prostate cancer cases diagnosed since May 1999 was derived exclusively from the Finnish Cancer Registry, which provides almost 100% case ascertainment (37). Information about disease stage was available for cases diagnosed through April 1999. Advanced cases ($n = 318$) were defined as those with stage III or IV of the tumor-node-metastasis (TNM) staging system, as defined by the American Joint Committee on Cancer (38). Prostate-specific antigen screening has not been widely adopted in Finland, and thus very few cases in the cohort were identified through this mechanism.

Statistical Analysis. Height was divided into approximate quintiles based on the distribution in the entire cohort. Although height was normally distributed in our population, many men had the same values, which prevented an even distribution of individuals across quintiles. Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for prostate cancer according to quintiles of height, with the lowest category assigned as the reference group. P values for linear trend were based on a quintile median scored variable modeled continuously. The proportional hazards assumption was tested and upheld using a cross-product term of person-years (natural log) and height (linear, continuous; $P = 0.82$).

Previously identified risk factors for prostate cancer were examined as potential confounders in the analysis, including age (years), weight (kg), BMI (kg/m^2), years smoked regularly, number of cigarettes smoked per day, residence (urban, rural), marital status (married, not married), education (\leq primary school, $>$ primary school), physical activity (reflecting both leisure and occupational activity), self-reported history of

physician-confirmed prostatomegaly [i.e., benign prostatic hyperplasia (BPH)], history of diabetes mellitus, family history of prostate cancer, and serum α -tocopherol concentrations. We also evaluated whether several dietary variables confounded the height-prostate cancer association, including daily intake of energy (kcal), alcohol (g), lycopene (μg), vitamin E (mg), red meat (g), phosphorus (mg), selenium (μg), calcium (mg), and vitamin D (μg). All dietary covariates were adjusted for energy intake using the residual method (39). Confounders were evaluated singly and in combination with each other to determine whether they produced a $>10\%$ change in relative risk estimates associated with height. Age was the only variable that met this criterion for confounding, and we therefore only present age-adjusted results.

Effect modification was evaluated through stratified analysis and by including cross-product terms between each exposure and height (continuous) in age-adjusted models. The following modifiers were categorized based on the median value in the entire cohort: age (<57 , ≥ 57 years), years smoked regularly (<36 , ≥ 36), and cigarettes per day (<20 , ≥ 20). History of prostatomegaly (BPH; no, yes), family history of prostate cancer (no, yes), personal history of diabetes mellitus (no, yes), physical activity level (inactive, moderately active, very active), and intervention assignment (α -tocopherol versus no α -tocopherol, β -carotene versus no β -carotene) were each evaluated as categorical variables. Stratification of results according to BMI (<25 , $\geq 25 \text{ kg}/\text{m}^2$) was based on the WHO recommended cut point that discriminates normal weight individuals from overweight individuals (40). A subset analysis based on disease stage (TNM stages I-II; III-IV) was conducted and tested statistically using a χ^2 test.

All P values are two sided, with statistical significance set a priori at a level of $\alpha = 0.05$. Statistical analyses were done using Statistical Analysis Systems (SAS) software, version 8.02 (SAS, Inc., Cary, NC).

Results

Age-adjusted baseline characteristics of study participants are shown in Table 1 according to quintiles of height. Taller men were younger, more likely to live in an urban area, to be married and better educated, and to have a history of BPH, diabetes, and/or a family history of prostate cancer compared with shorter men. They also weighed more, had higher energy intake, and consumed more alcohol, lycopene, vitamin E, and selenium, and less fat, red meat, phosphorus, and calcium than shorter men. With the exception of BMI, serum α -tocopherol concentrations, and physical activity, the trend across quintiles of height was statistically significant for all baseline characteristics, independent of age ($P < 0.05$).

HRs and 95% CIs for the association between incident prostate cancer and height are presented in Table 2. Age-adjusted estimates indicated a statistically significant 30% elevation in risk for men in the fourth quintile of height (i.e., 176-178 cm) and a smaller elevation in the fifth quintile (i.e., 179-200 cm). The HR of prostate cancer per 10-cm increment in height was 1.08 (95% CI, 0.99-1.18; $P_{\text{trend}} = 0.08$).

Figure 1 details the association between height and prostate cancer according to disease stage. Height was a strong predictor of advanced stage disease (TNM stages III-IV; for highest versus lowest quintile of height, HR, 2.02; 95% CI, 1.37-2.97; $P_{\text{trend}} = 0.0008$), but not of less aggressive prostate cancers (TNM stages 0-II; HR, 0.88; 95% CI, 0.68-1.14; $P_{\text{trend}} = 0.94$).

Stratification by other selected risk factors revealed only modest effect modification (Table 3). The height-prostate cancer relationship seemed to be stronger among those without a history of BPH or diabetes, longer-term smokers, older individuals, and those with a family history of prostate cancer; however, all P values for interaction were >0.05 .

Table 1. Age-adjusted means and proportions of baseline characteristics by quintile of height in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

	Quintile of height (cm)				
	1 (136-168)	2 (169-171)	3 (172-175)	4 (176-178)	5 (179-200)
No. individuals	5,874	4,966	7,405	4,724	6,150
Median height, cm	166	170	174	177	181
Age, y	58.4	57.5	57.3	56.8	56.1
BMI, kg/m ²	26.2	26.4	26.3	26.3	26.2
Weight, kg	71.4	76.3	79.2	82.4	87.0
Years smoked	36.2	36.1	35.8	35.9	35.8
Cigarettes/d	19.8	20.3	20.4	20.7	20.9
Urban residence, %	38.8	40.6	41.8	44.1	46.6
Married, %	75.9	80.5	80.7	81.2	82.8
Education >primary school, %	25.0	30.2	33.9	39.5	44.2
Physical activity level,* %					
Inactive	26.4	24.3	24.8	25.0	24.3
Moderately active	41.7	42.5	43.1	43.5	44.6
Very active	29.2	30.4	29.4	28.6	28.2
History of prostatomegaly (BPH), %	2.8	3.3	3.3	3.1	3.6
History of diabetes mellitus, %	3.7	4.3	4.3	3.9	4.8
Family history of prostate cancer, [†] %	2.8	3.0	3.1	4.2	3.8
Serum α -tocopherol, [‡] mg/L	11.9	11.9	11.9	12.0	12.0
Daily dietary intake [§]					
Energy, kcal	2,719	2,774	2,820	2,839	2,914
Alcohol, g	17.2	17.8	17.9	18.6	18.6
Fat, g	106	106	106	105	105
Lycopene, μ g	699	752	801	830	880
Vitamin E, mg	11.7	11.7	12.1	12.3	12.4
Red meat, g	149	148	146	144	143
Phosphorus, mg	2,168	2,173	2,156	2,151	2,146
Selenium, μ g	89.2	89.8	89.7	89.6	90.5
Calcium, mg	1,412	1,423	1,396	1,384	1,377
Vitamin D, μ g	5.37	5.38	5.48	5.60	5.63

*Available for 29,062 individuals.

[†] Available for 18,527 individuals (918 cases).[‡] Available for 29,088 individuals.[§]Based on the 27,098 individuals with complete dietary data; all dietary variables are energy adjusted, except for calories and alcohol.^{||}Includes beef, pork, sausages and other cold cuts, and inner organs and blood.

Discussion

Our analysis revealed a weak, yet statistically significant, association between greater adult height and prostate cancer risk in male smokers. Analysis by tumor stage indicated a striking 2-fold increased risk in taller men for advanced disease, but no increase in risk for less aggressive prostate cancers. We did not find significant effect modification by other examined exposures, although the association seemed to be stronger in older men, heavier smokers, and those without a history of BPH or diabetes, and there was an approximate doubling of risk among men with a positive first-degree family history of prostate cancer.

Our study was conducted in a relatively homogeneous cohort of white Finnish male smokers, which limits the generalizability of our findings to nonsmokers and other races and ethnicities. This homogeneity also adds strength to the study, however, in that differences in height may be influenced to a proportionally greater degree by variations in environmental exposures (particularly nutrition), as compared with

heredity and socioeconomic factors (41). In fact, five of the seven prospective studies that yielded positive associations between height and prostate cancer risk were conducted in cohorts that were relatively homogeneous with respect to ethnicity alone (28) or both ethnicity and social class (27, 29, 30, 32). An additional minor limitation is that measured height may not have reflected maximal adult height in our study population because taller men tended to be younger, and it is known that standing height decreases with advancing age (42). Any bias from this source would likely be nondifferential and therefore attenuate any true association between height and prostate cancer risk.

There are several notable strengths of our study. The large number of cases available for analysis ensured adequate power to detect a small yet biologically meaningful increase in prostate cancer risk with increasing height, and to evaluate the association by disease stage. Another important advantage of our study is that height was measured in a standardized manner by specially trained nurses, rather than being self-reported. This avoids the misclassification and potential bias

Table 2. Age-adjusted HRs and 95% CIs for incident prostate cancer according to quintiles of height in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (1985-2002)

	Quintile of height (cm)					<i>P</i> _{trend}
	1 (136-168)	2 (169-171)	3 (172-175)	4 (176-178)	5 (179-200)	
No. cases	251	230	345	248	272	
Person-years	69,959	60,924	91,905	59,049	78,599	
Crude incidence rate (per 1,000 men)	42.73	46.31	46.59	52.50	44.23	
Age-adjusted HR (95% CI)	1.00 (reference)	1.11 (0.93-1.32)	1.11 (0.95-1.31)	1.30 (1.09-1.55)	1.14 (0.96-1.35)	0.04

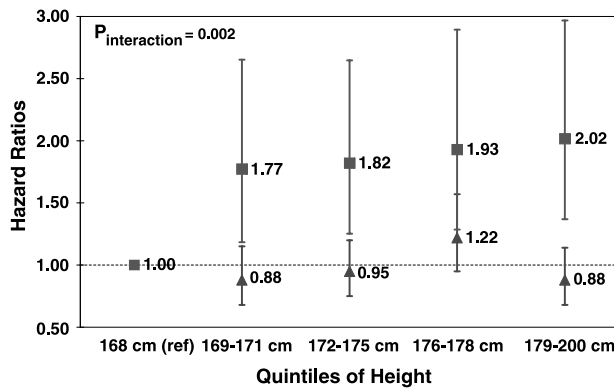


Figure 1. Age-adjusted HRs and 95% CIs for prostate cancer risk according to quintiles of height, stratified by disease stage. \blacktriangle , stages I to II; $P_{\text{trend}} = 0.94$. \blacksquare , stages III to IV; $P_{\text{trend}} = 0.0008$. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (1985-2002).

from shorter men overestimating their height (43). Data were available for an extensive number of potential confounders in our analysis, including known and putative risk factors for prostate cancer, and only age confounded the height-prostate cancer association, according to a priori criteria. It is therefore unlikely that residual confounding materially influenced our findings, although the effect of unmeasured characteristics is unknown.

A positive association between height and prostate cancer has been observed in several, although certainly not all, prospective studies to date. Of 18 prospective cohort studies published to date, 11 showed no association (34, 35, 41, 44-51) and 7 showed statistically significant elevations in risk with increasing height (27-33). Risk increases in the latter studies

varied from 20% to 80% for men in the highest versus the lowest quantile of height. The largest study to date detected a significant association (tallest versus shortest men, HR, 1.72; 95% CI, 1.46-2.04) and showed the strongest dose-response relationship ($P_{\text{trend}} < 0.0001$) of any cohort study (28).

Associations between height and clinically relevant prostate cancer have been examined (16, 21, 24, 29-31, 33-35), with stronger associations observed for more advanced versus localized disease in several studies (24, 29-31), which is in accord with the present findings. For example, a particularly strong association between tallness and aggressive prostate cancer was noted in the Auckland Prostate Study for men taller than 179 cm who also had a positive family history of prostate cancer, although stratum-specific sample sizes were small (HR, 7.41; 95% CI, 1.68-32.67; $P_{\text{trend}} = 0.02$; ref. 24).

Although the biological mechanisms linking adult stature and prostate cancer risk are not known, mediation by endocrine effects is considered a likely possibility. Height is influenced by early life nutrition, heredity, and cumulative exposure to growth factors, sex steroids, and other hormones in the hypothalamic-pituitary axis during growth and development. Excess energy intake relative to expenditure, as well as exposure to higher levels of circulating androgens during periods of growth, is associated with increased levels of IGF-I, a growth-promoting hormone that has been shown to enhance carcinogenesis via increased cell proliferation and cancer cell survival (52). These factors also influence growth velocity and maturation, supporting tallness as a marker of higher cumulative exposure to IGF-I and sex steroids, particularly during puberty. It is during this same period that the prostate gland develops rapidly along with body height (53, 54), such that height may correlate with prostate gland size, with taller men having greater glandular volumes and, therefore, a larger number of proliferating cells that are at risk of mutation and transformation (55). Why height may be more associated with risk of developing advanced

Table 3. Age-adjusted HRs and 95% CIs for prostate cancer according to quintiles of height, stratified by selected factors, in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (1985-2002)

	Quintile of height (cm)										P_{trend}
	1 (136-168)		2 (169-171)		3 (172-175)		4 (176-178)		5 (179-200)		
	No. cases	HR (reference)	No. cases	HR (95% CI)	No. cases	HR (95% CI)	No. cases	HR (95% CI)	No. cases	HR (95% CI)	
Age, y											
<57	75	1.00	82	1.11 (0.81-1.52)	130	1.12 (0.84-1.48)	93	1.16 (0.86-1.58)	120	1.04 (0.78-1.39)	0.82
≥57	176	1.00	148	1.10 (0.88-1.37)	215	1.11 (0.91-1.35)	155	1.38 (1.11-1.71)	152	1.21 (0.97-1.50)	0.02
BMI, kg/m ²											
<25	92	1.00	89	1.24 (0.93-1.66)	128	1.16 (0.89-1.51)	98	1.48 (1.11-1.97)	100	1.17 (0.88-1.55)	0.16
≥25	159	1.00	141	1.03 (0.82-1.29)	217	1.09 (0.89-1.33)	150	1.20 (0.96-1.50)	172	1.12 (0.90-1.39)	0.15
Cigarettes/d											
<20	126	1.00	93	0.92 (0.71-1.21)	135	0.92 (0.72-1.17)	106	1.22 (0.95-1.59)	115	1.07 (0.83-1.38)	0.24
≥20	125	1.00	137	1.29 (1.01-1.16)	210	1.31 (1.05-1.63)	142	1.39 (1.09-1.77)	157	1.22 (0.97-1.55)	0.09
Years smoked											
<36	94	1.00	78	0.91 (0.68-1.23)	141	1.03 (0.79-1.34)	103	1.19 (0.90-1.57)	113	0.94 (0.72-1.24)	0.80
≥36	157	1.00	152	1.23 (0.99-1.54)	204	1.16 (0.94-1.43)	145	1.36 (1.09-1.71)	159	1.29 (1.03-1.61)	0.02
Family history of prostate cancer*											
No	168	1.00	145	1.02 (0.81-1.27)	227	1.05 (0.86-1.29)	157	1.16 (0.93-1.44)	156	0.91 (0.73-1.30)	0.75
Yes	6	1.00	9	1.56 (0.55-4.39)	19	2.19 (0.87-5.48)	13	1.78 (0.67-4.69)	18	2.10 (0.83-5.34)	0.14
History of prostatomegaly (BPH)											
No	234	1.00	218	1.14 (0.95-1.37)	322	1.12 (0.95-1.33)	235	1.32 (1.10-1.58)	256	1.16 (0.97-1.39)	0.04
Yes	17	1.00	12	0.72 (0.34-1.50)	23	0.97 (0.52-1.81)	13	0.99 (0.48-2.03)	16	0.89 (0.45-1.76)	0.99
History of diabetes mellitus											
No	241	1.00	222	1.11 (0.93-1.34)	331	1.11 (0.94-1.32)	243	1.32 (1.11-1.58)	262	1.15 (0.96-1.37)	0.03
Yes	10	1.00	8	0.94 (0.37-2.40)	14	1.07 (0.47-2.40)	5	0.72 (0.25-2.12)	10	0.86 (0.36-2.07)	0.66
Physical activity											
Inactive	76	1.00	72	1.28 (0.93-1.77)	108	1.24 (0.92-1.66)	66	1.27 (0.91-1.76)	72	1.22 (0.88-1.69)	0.25
Moderately active	108	1.00	102	1.12 (0.85-1.47)	151	1.12 (0.87-1.43)	111	1.32 (1.01-1.72)	126	1.16 (0.90-1.51)	0.14
Very active	67	1.00	54	0.89 (0.62-1.27)	86	0.97 (0.71-1.34)	71	1.28 (0.92-1.79)	74	1.01 (0.73-1.41)	0.40

*Based on 18,527 individuals.

prostate cancer could be related to the role of IGFs in tumor growth, invasion, and metastases, a role supported by a recent study of IGF-I and IGF binding protein 3 (56). In the study by Chan et al., men with simultaneously high levels of IGF-I and low levels of IGF binding protein 3 had more than nine times the risk of advanced-stage prostate cancer when compared with those individuals with the lowest levels of both proteins.

In summary, we found a weak positive relationship between adult height and the risk of total prostate cancer, although the association was much stronger for advanced tumors. Elucidation of the underlying biological processes may enhance our understanding of the interrelationships among growth factors, hormones, and risk of this common malignancy.

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